Opportunities and Challenges in Developing Recombinant Human Antithrombin for Treatment of Hereditary AT Deficiency

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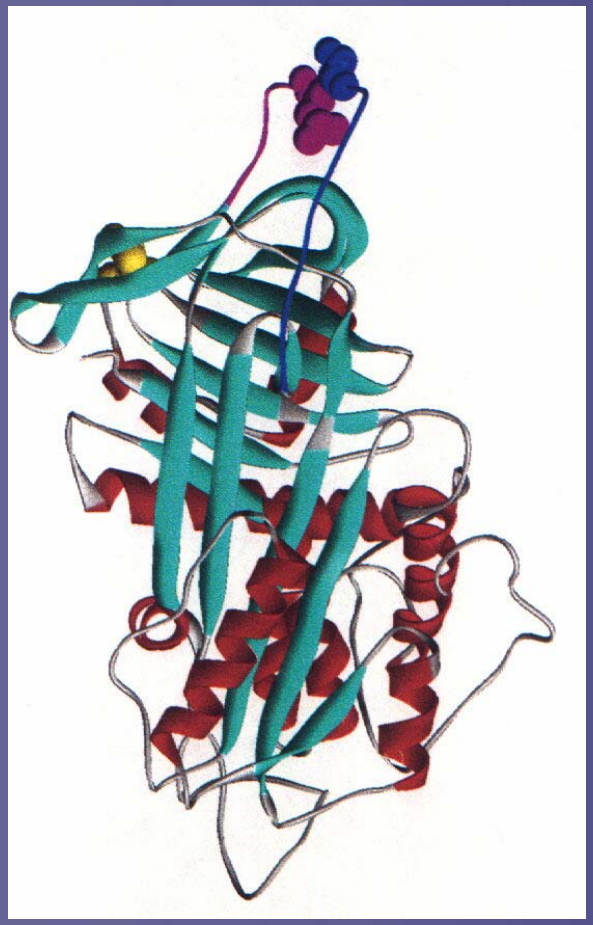
Antithrombin



- **Single Chain Glycoprotein**
  - 432 amino acids, Peptide MW 49,670
  - 4 N-linked glycosylation sites
  - 6 cysteine residues, 3 disulfide bonds
- **Serine Proteinase Inhibitor**
  - Inhibits Thrombin and Factor Xa
  - Binding of heparin causes a conformation change and 1000 fold increase in inhibitory activity
- **Therapeutic Indications**
  - Acquired AT deficiencies
  - **Hereditary AT deficiency in high risk situations (prevention of thromboembolic events)**

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Recombinant Human Antithrombin

- Antithrombin alfa (INN)
- Produced and purified from the milk of transgenic goats
  - Closed herd of goats maintained in U.S.
  - Expression of protein into milk regulated by a mammary gland promoter (~1-4 g/L)
  - Purified by filtration & chromatography steps, includes viral inactivation step
  - Robust viral & TSE validation of purification process

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Recombinant Production

Characteristic	Recombinant AT	Human Plasma Derived AT
Source	Milk	Plasma
[AT] (mg/mL)	2.0 – 4.0	0.125
Vol./donation (mL)	750	275
Max donations/year	600	1 - 4
Vol.(L)/Donor/Year	450	0.275 - 1.1
Donors / Kg Drug Substance*	1-2	~14,500- 58,000

* Assumes 50% yield through purification

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Hereditary AT Deficiency

- Plasma AT levels < 60%
- AT supplementation needed only during high risk situations (e.g., surgery, labor/delivery)
- Published prevalence estimates
  - Range: 1 in 2,000 to 1 in 5,000
- Estimated patient population
  - Europe: 175,000
  - United States: 150,000
    - A rare condition
- Frequency of treatment
  - Pregnancy
  - Surgery
    - Infrequent treatment of patients with a rare condition

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Europe

- EMEA Note for Guidance Documents
  - Clinical Investigation of Antithrombin Products (CPMP/BPWG/2220/99)
  - Clinical Investigation of Products for Treatment of Venous Thromboembolic Disease (CPMP/EWP/563/98)
  - Clinical Investigation of Products for Prevention of Intra- and Post-operative Venous Thromboembolic Risk (CPMP/EWP/707/98)
- Clinical development of Antithrombin
  - Pharmacokinetic study in hereditary AT deficient patients (not during high risk situation)
  - Open label safety & efficacy study
    - Objective measure of efficacy

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Europe

- Scientific Advice
  - Pharmacokinetic study in hereditary AT deficient patients
  - Open label safety & efficacy trial in at least 12 patients
    - Objective measure of efficacy
      - Independent review of ultrasound imaging data
    - Non-zero event rate to be carefully explained

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Multinational Safety & Efficacy Trial

- Population
  - 15 hereditary AT deficient patients
    - Documented AT activity ≤ 60% *and*
    - Personal or family history of thromboembolic complications
  - Scheduled for elective procedure providing a high risk situation
    - Surgery
    - Cesarean section
    - Induced/spontaneous delivery
- Objectives
  - Efficacy
    - Assess incidence of DVT
    - Assess incidence of 'other' thromboembolic complications
  - Safety (AEs and immunogenicity)

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Patient Recruitment

- Multinational effort (16 countries)
- >23,000 physicians contacted
- ~500 physicians who have had HD patients in their practice at some time
  - Physicians notified about our study to enable recruitment
- Patient recruitment period: 18 months

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Patient Recruitment Effort

Enrolling Countries (6)	Number Sites	Number Pts ID'd	Number Pts Enrolled
USA	22	26	3
Italy	6	8	1
UK	5	7	2
Germany	5	15	5
France	4	8	2
Sweden	3	4	1
Others *	11	14	0
TOTALS	**55**	**82**	**14****

*Czech, Hung, Ire, Switz, Nor, Sp, NL, Israel
** 17% of identified patients enrolled

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Europe

- Clinical development timeline
  - 28 months (FPI PK → LPO safety & efficacy)
- MAA submitted January 2004
- Responding to List of Outstanding Issues (July 2005)

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United States

- Adequate & well-controlled trial required
  - Placebo-controlled?
    - Ruled out, known high risks to patients & large sample sizes
  - Active comparator (superiority or non-inferiority)?
    - No AT (standard of care?)
      - Ruled out, Phase II → Phase III
    - AT (non-inferiority)
      - Ruled out, large sample size & availability of comparator product?
  - Historical control?
    - AT (non-inferiority)

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United States

- Historical controlled trial
  - Only feasible study design option
  - Comparator – hpAT treated patients
    - Multinational effort to identify sites & collect data from medical charts
  - Additional rhAT treated patients (n=17) needed for comparison of rhAT & hpAT
    - Multinational effort to recruit patients
  - Study is underway in U.S.

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